JUL 09 2007
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Dasch *et al.*	Art Unit: 1616
Appl. No.: 10/681,571	Examiner: E. Webman
Filed: October 8, 2003	Atty. Docket: 00166.2040-US01
For: **Method of Modifying the Release Profile of Sustained Release Compositions**	

Declaration of Elliot W. Ehrich, M.D. Under 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Elliot W. Ehrich, M.D., hereby declare and state as follows.

1. I have a Bachelor's degree in Biochemistry, and a Doctorate degree in Medicine. I have over fourteen years experience in the biotechnology and pharmaceutical industries. I am currently employed by Alkermes, Inc. ("Alkermes") as Senior Vice President, Research and Development, Chief Medical Officer. I have been employed by Alkermes or their predecessor in business for more than seven years. A copy of my *curriculum vitae* is attached.

2. The above-captioned U.S. Patent Application No. 10/681,571 ("the '571 application") is owned by Alkermes Controlled Therapeutics Inc., a subsidiary of Alkermes. I have read and understood the '571 application. I am familiar with the technology of the invention disclosed in the '571 application through my education and my work at Alkermes.

3. I have read and understood the Office Action dated April 9, 2007 that has issued in the '571 application. I have also read and understood U.S. Patent No. 5,707,644 ("the '644 patent") that is referred to in the Office Action. Page 2 of the Office Action states that "[I]t

would have been obvious to one of ordinary skill in the art to add exendin to the composition of Illum [the '644 patent] containing insulin to achieve the benefical [sic] effect of an additional anti-diabetic agent." For at least the following reasons, I respectfully disagree with the Examiner's position that the addition of exendin to an insulin formulation such as that disclosed in the '644 patent would have achieved a "beneficial effect of an additional anti-diabetic agent."

4. The '644 patent is directed to a drug delivery composition for intranasal delivery that includes a plurality of bioadhesive microspheres and a systemically active drug. One of the listed drugs is insulin. '644 Patent, Col. 2, Lines 22-32; Col. 7, Lines 26-27; Abstract. However, the '644 patent makes no mention of exendin.

5. Administration of insulin requires dose titration to achieve clinical glycemic goals. Insulin is administered in as units, and the amount of titration required (i.e. the specific number of units administered) is dependent upon the patient's blood glucose level and dietary intake. Hypoglycemia is the adverse clinical side effect associated with the inaccurate titration of insulin.

6. In contrast to insulin, exendin is not a titratable drug; exendin is a fixed dose drug. In general, when a drug requiring titration, such as insulin, is administered in a combination therapy with a fixed dose drug, the patient will underdose or overdose on the fixed dose drug. Therefore, administering insulin, a drug requiring titration, with exendin, a fixed dose drug, will cause the patient to underdose or overdose on exendin. Overdosing of exendin will result in hypoglycemia and/or nausea. Underdosing of exendin will result in hyperglycemia and/or an increased risk of complication associated with diabetes. For at least these reasons, the addition of exendin to an insulin formulation such as that disclosed in the '644 patent would not, contrary

to the Examiner's assertion, have achieved a "beneficial effect of an additional anti-diabetic agent."

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United Sates Code and that such willful false statements may jeopardize the validity of the above-captioned patent application or any patent issued thereon.

Elliot W. Ehrich, M.D.

Date: 7/2/2007

Elliot W. Ehrich, MD

Alkermes, Inc.
88 Sidney Street
Cambridge MA, 02139
Phone 617 583 6190
elliot.ehrich@alkermes.com
www.alkermes.com

- Senior Vice President Research and Development, Chief Medical Officer 2007-Present
- Vice President, Science and Development, Chief Medical Officer 2003-2007
- Vice President, Medical Affairs 2000-2003

Responsible for project management and all research and development functions (~200 scientists and professionals). Successful registration – RISPERDAL CONSTA®, VIVITROL®. Multiple candidates in active development.

PRIOR EMPLOYMENT

Merck & Co., Inc. 1993-2000

- Senior Director, Clinical Research, 1998 - 2000
- Director, Clinical Research 1995 - 1998
- Associate Director, Clinical Pharmacology 1993 –1995

Directed clinical development group (group size ~50) in areas of dermatology, arthritis, pain and oncology including successful registration and marketing of products in arthritis and asthma.

- World-wide project team leader, Commercialization Team Leader

EDUCATION

SCHOOL	DATE	MAJOR	DEGREE
Princeton University Princeton, NJ	1977 - 1981	Biochemistry	B.A., *Magna cum Laude, Phi Beta Kappa*
Columbia University College of Physicians and Surgeons, New York, NY	1982 - 1986	Medicine	M.D.

POSTGRADUATE TRAINING

Stanford University, Stanford, CA 1986 - 1993

Internship and Residency, Department of Medicine
Fellowship, Departments of Medicine, Division of Immunology and Rheumatology

European Molecular Biology Laboratory (EMBL) 1981, 1985
Heidelberg, Germany, Research Assistant

ACADEMIC APPOINTMENT

Clinical Assistant Professor of Medicine 1997-Present
Robert Wood Johnson Medical School

PROFESSIONAL HONORS

Fellow, American College of Rheumatology 1993 - Present
American College of Rheumatology Senior Rheumatology Scholar Award
Cancer Research Institute/FW. Kirby Foundation Fellowship 1990-1993
Board Certification, Rheumatology, American Board of Internal Medicine 1993-2003
Board Certification, Internal Medicine, American Board of Internal Medicine 1989-Present
Board Certification, National Board of Medical Examiners 1986-Present

PUBLICATIONS

Dunbar JL, Turncliff RZ, Dong Q, Silverman BL, Ehrich EW, Lasseter KC. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. Alcohol Clin Exp Res. 2006 Mar;30(3):480-90.

Turncliff RZ, Dunbar JL, Dong Q, Silverman BL, Ehrich EW, Dilzer SC, Lasseter KC. Pharmacokinetics of long-acting naltrexone in subjects with mild to moderate hepatic impairment. J Clin Pharmacol. 2005 Nov;45(11):1259-67.

Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BS, Loewy JW, and Ehrich EW, (2005), Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence, *JAMA*, 293(13): 1617-1625.

Johnson B, Ait-Daoud-Tiouririne N, Aubin H-J, van den Brink W, Guzzetta R, Loewy J, Silverman B, and Ehrich E, (2004), A Pilot Evaluation of the Safety and Tolerability of Repeat Dose Administration of Long-Acting Injectable Naltrexone (Vivitrex®) in Patients with Alcohol Dependence. *Alcohol Clin Exp Res,*28(9):1356-61.

Bolognese JA, Schnitzer TJ, Ehrich EW, (2003), Response Relationship of Visual Analog and Likert Scales in Osteoarthritis Efficacy Measurement. *Osteoarthritis and Cartilage,* 11(7):499-507

Emery P, Kong SX, Ehrich EW, Watson DJ, Towheed TE (2002). Dose-effect relationships of nonsteroidal antiinflammatory drugs. *Clinical Therapeutics*, 24(8):1225-1291

Bolognese, J, Ehrich, E, and Schnitzer T (2001) Precision of Composite Measures of Osteoarthritis Efficacy in Comparison to That of Individual Endpoints. *Journal of Rheum,* 28:2700-4

L. DeTora, D. Krupa, J. Bolognese, R. Sperling, and E. Ehrich (2001) Rofecoxib Shows Consistent Efficacy in OA Clinical Trials, Regardless of Specific Patient Demographic and Disease Factors. *Journal of Rheum,* 11:2494-503

PUBLICATIONS Cont.

K. Truitt, R. Sperling, W Ettinger, M Greenwald, L DeTora, Q Zeng, J Bolognese and E. Ehrich, (2001) A multicenter, randomized, controlled trial of rofecoxib in advanced elderly patients with osteoarthritis. *Aging Clin Exp Res, 13:* 112-121.

Ehrich E., J. Bolognese, D. Watson, and S. Kong, (2001) Effect of Rofecoxib on Measures of Health-Related Quality of Life in Patients with Osteoarthritis. *American Journal of Managed Care,* 7:606-16.

Vignon E, Garnero P, Delmas P, Avouac B, Bettica P, Boers M, Ehrich E, MacKillop N, Rovati L, Serni U, Spector T, Reginster JY. (2001) Recommendations for the registration of drugs used in the treatment of osteoarthritis: an update on biochemical markers. *Osteoarthritis Cartilage.* 9:289-93

Ehrich, E, G. Davies, D. Watson, J. Bolognese, B. Seidenberg and N. Bellamy (2000) Minimal Perceptible Clinical Improvement with the Western Ontario and McMaster Universities Osteoarthritis Index Questionnaire and Global Assessments in Patients with Osteoarthritis. *J Rheum 27:* 2365-2341

R. Day, B. Morrison, D van der Heijde, Q. Zeng, J. Bolognese, B. Daniels, B. Seidenberg, and E. Ehrich (2000): Efficacy and Safety of rofecoxib, a COX-2 specific inhibitor, compared with ibuprofen in the treatment of osteoarthritis of the knee and hip. Arch Int Med, 26;160:1781-7.

M. Depré, E. Ehrich, A. Van Hecken, I. De Lepeleire, A. Dallob, P. Wong, A. Porras, B.J. Gertz, and P.J. De Schepper: (2000) Pharmacokinetics, COX-2 Specificity, and Tolerability of Supratherapeutic Doses of Rofecoxib in Humans. European Journal of Clinical Pharmacology 56(2):167-74.

Elliot Ehrich, Thomas J. Schnitzer, Harris McIlwain, Robert Levy, Frederick Wolfe, Michael Weisman, Qi Zeng, Briggs Morrison, James Bolognese, Beth Seidenberg, and Barry J. Gertz (1999): Effect of Specific COX-2 Inhibition in Osteoarthritis of the Knee: A 6-week Double-blind, Placebo-controlled, Pilot Study of Rofecoxib. *J Rheum,26:*2438-2447.

Cannon GW, J Caldwell, P Holt, B McLean, B Seidenberg, J Bolognese, E Ehrich, S Mukhodpadyay, and B. Daniels (2000): Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. Arthritis Rheum. 2000 May;43(5):978-87.

Thomas Schnitzer, Ken Truitt, Roy Fleishman, Paul Dalgin, Joel Block, Qi Zeng, James Bolognese, Beth Seidenberg, and Elliot Ehrich (1999). A Double-blind placebo-controlled, trial to evaluate the safety, tolerability, and effective dose range of rofecoxib in patients with rheumatoid arthritis. *Clin Ther, 21:*1688-1702.

Elliot Ehrich, Aimee Dallob, Inge DeLepeleire, Denis Riendeau, Weiying Yuan, Arturo Porras, Johanna Wittreich, James R. Seibold, Paul De Schepper, Donald Mehlisch, Barry J. Gertz (1999): Characterization of Rofecoxib as a Cyclooxygenase-2 isoform inhibitor and Demonstration of Analgesic Efficacy in the Dental Pain Model. *Clinical Pharmacology and Therapeutics, 65:*336-47.

P. Brooks, P Emery, J. Evans, H. Fenner, C.J. Hawkey, C. Patrono, J. Smolen, F. Breedveld, R. Day, M. Dougados, E.W. Ehrich, J. Gijon-Banos, T. Kvein, M.H. Van Rijswijk, T. Warner, and H. Zeidler (1999): Interpreting the significance of the differential inhibition of cyclooxygenase-1 and cylcooxygenase-2. Rheumatol (Oxf). 1999;38: 779-788.

PUBLICATIONS Cont.

Christine Brideau, Stacia Kargman, Susana Liu, Aimee Dallob, Elliot Ehrich, Ian W. Rodger, and Chi-Chung Chan (1996): A human whole blood assay for clinical evaluation of biochemical efficacy of cyclooxygenase Inhibitors. *Inflamm Res 45: 68-74.*

Hansjorg Schild, Nassim Mavaddat, Christa Litzenberger, Elliot Ehrich, Mark M. Davis, Louis Matis, Rockford K. Draper, and Yueh-hsiu Chien (1994): The Nature of MHC recognition by □□ T Cells. *Cell*, 76:29-37.

Ehrich, Elliot W., Brigitte Devaux, Jeffery L. Jorgensen, Y.S. Chien and Mark M. Davis (1993): T Cell Receptor Recognition of Peptide/MHC and superantigen/MHC Complexes are dominated by antigen. *J. Exp. Med.*, 178: 713-722.

Jorgensen, Jeffery L., Phillip A. Reay, Elliot Ehrich, and Mark M. Davis (1992): Molecular Components of T Cell Recognition, *Annual Review of Immunology*, 10: 835-73.

Ehrich, Elliot W., James L. McGuire, Youn H. Kim (1992): Association of Granuloma Annulare with Sarcoidosis. *Archives of Dermatology*: 128:855-6.

Ehrich, Elliot W., R. Elaine Lambert, James L. McGuire: Therapy of Immune Mediated Rheumatic Disease. In Melmon, K, H. Morelli, B Hoffman and D. Nierenberg (eds): Clinical Pharmacology, Basic Principles in Therapeutics, Third Edition (1991), J.D. Lippincott, New York.

Ehrich, Elliot W., James L. McGuire, Hugh O. McDevitt (1990): A Late Relapse of Wegener Granulomatosis (Letter), *Annals of Internal Medicine,* 112: 965.

Ehrich, Elliot, Alister Craig, Annemarie Poustka, Anna-Maria Frischauf and Hans Lehrach (1987): A Family of Cosmid Vectors with the Multi-Copy R6K Replication Origin, *Gene*, 57:229-237.

A Poustka, T Pohl, D Barlow, G Zehetner, A Craig, F Michiels, E Ehrich, A-M Frischauf, and H Lehrach (1986): Molecular Approaches to Mammalian Genetics, *Cold Spring Harbor Symposium on Quantitative Biology*, 51:131-139.